REMARKS

Status of the Claims

Claims 1-26 were originally filed in this application. Applicants have amended claims 1 and 8 to solely to change the grammatical form of the phrase "which may be straight-chain or branched" in the descriptions of the R^1 and R^2 groups, to "which is straight-chain or branched." This amendment does not alter the scope of the pending claims. Applicants have also amended claim 8 to recite that R^3 is a "carbonyl or thioamide group," as discussed below. This amendment is supported by the application as a whole, for example, at page 10, lines 4-13, of the specification. These amendments are directed to matters of form, and do not introduce new matter or require a further search of the art.

Applicants acknowledge that the Office finds claims drawn to a conjugate comprising F3 as an aryl group, oligonucleotides as the compounds to be transported, and a carboxylic acid as a reactive function, to be novel and nonobvious. (Office Action, pages 2-3; claim 9.)

The Office continues to hold claims 3, 6, and 7 withdrawn, asserting that they embrace species other than those that Applicants have provisionally elected (i.e., molecules to be transported are other than oligonucleotides). (Office Action at page 2; Election of Species Requirement mailed September 25, 2001.) Under 37 C.F.R. § 1.146, the Office has a duty to examine the non-elected subject matter of these claims to the extent necessary to determine the patentability of the generic claims. M.P.E.P. § 803.02. Applicants respectfully request that the Office carry out this examination with regard to the withdrawn claims.

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Claims 22-24 Are Enabled

The Office contends that claims drawn to a "pharmaceutical composition" comprising the conjugates of claims 1 and 8, and processes of preparing such compositions are not enabled. (Office Action at pages 3-16.) The Office also defines "pharmaceutical" use to include *in vivo* diagnosis as well as treatment, and contends that use of the claimed pharmaceutical compositions as "*in vivo* diagnostics" is also not enabled. Applicants respectfully traverse this rejection.

The Office again contends that Applicants' specification does not provide sufficient guidance regarding pharmaceutically active oligonucleotides and that the effectiveness of oligonucleotide therapeutics is unpredictable. However, Applicants have not claimed pharmaceutically active oligonucleotides themselves, but a genus of conjugating groups that may be attached to known pharmaceutically active oligonucleotides to increase their cellular uptake and enhance their effectiveness. Because claims 22-24 are restricted to compositions in which the molecule to be transported is known to have pharmaceutical activity, enablement of these claims does not turn on whether oligonucleotides, or other molecules to be transported, by themselves have predictable therapeutic effects.

Instead, the present specification, in conjunction with the prior art, simply must enable one of ordinary skill in the art to prepare conjugated compositions with greater efficacy than the un-conjugated compositions. This may be achieved if the conjugates have increased cellular uptake over the un-conjugated compositions, allowing them to reach their cellular targets more effectively.

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Moreover, the patentability of a pharmaceutical composition does not require that the composition ultimately be successful in clinical trials. Rather, a pharmaceutical composition is patentable if there is a reasonable correlation of *in vitro* or *in vivo* model data in the specification and prior art with a therapeutic activity. M.P.E.P. §§ 2164.02 and 2107.01(III); *Cross v. Iizuka*, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Brana*, 34 U.S.P.Q.2d 1436, 1442-3 (Fed. Cir. 1995). A rigorous or exact correlation is not required. *Cross v. Iizuka*, 224 U.S.P.Q. 739 (Fed. Cir. 1985).

This correlation standard recognizes that lengthy or complex experimentation may still be needed before a pharmaceutical composition may be useful as a human therapeutic. M.P.E.P. § 2164.01. Indeed, the Federal Circuit has explained that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a model has made a significant contribution to the art, even when the compound turns out not to be useful in human treatment. *Brana*, 34 U.S.P.Q.2d at 1442.

In accordance with this standard, Applicants' specification demonstrates that oligonucleotide conjugates according to the claimed invention show increased cellular uptake and pharmaceutical efficacy in cell culture. For instance, Example 7 and Tables 1-3 show that fluorescence from FDA-labeled CO_1 and CO_3 oligonucleotides, which are conjugates according to the invention, is moderate to strong after 120 minutes of incubation with mammalian, insect, fungal, and prokaryotic cells. In contrast, these cells do not generally take up fluorescein-labeled oligonucleotides of the same sequence that have not been prepared as conjugates according to the invention. (*Id.*) Example 16 and Table 5 show that mammalian REH cells effectively take up 20, 50, and 80-mer

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oligonucleotides that have been modified according to the invention. Further, Example 17, Figure 9, and Table 4 show that a claimed oligonucleotide conjugate inhibited tumor cell growth in culture.

The Office provides no evidence to support a conclusion that such *in vitro* assays cannot be correlated with increased *in vivo* cellular uptake according to the correlation standard of M.P.E.P. §§ 2164.02 and 2107.01(III). Therefore, it has failed to produce a *prima facie* case of nonenablement. The Office has the initial burden to produce substantial evidence showing that one of ordinary skill in the art would not correlate the cell culture data in the specification with increased *in vivo* uptake of a conjugated oligonucleotide. *See In re Zurko*, 258 F.3d 1379, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001).

Applicants also note that, while the Office's focus on the predictability of un-conjugated antisense oligonucleotides is not relevant in considering the enablement of claims 22-24, the Office uses too high a standard in judging their predictability. The Office seems to contend that few, if any, such oligonucleotides are "pharmaceutically active." For example, the Office comments that "there were no known scientific laws that enabled the accurate prediction of which antisense molecules would have pharmaceutical effect." (Office Action at page 11.) Yet, according to a search of the Aurigin® patent database, the Office had already issued 76 patents with claims reciting "pharmaceutical compositions" comprising "antisense" oligonucleotides prior to Applicants' filing date. This illustrates that there were a variety of patented, pharmaceutically active oligonucleotides with which this invention could be practiced at the time this application was filed, regardless of how easy or difficult it had originally been to predict the pharmaceutical effectiveness of those oligonucleotides.

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The Office also comments that "Applicants' [previous] assertion that it is reasonable to conclude that compounds in phase II and III clinical trials are pharmaceutically effective is unsupported." (Office Action at page 10.) Here, the Office seems to contend that success in clinical trials is required before a compound can be "pharmaceutically active." Yet, this is contrary to both the correlation standard of M.P.E.P. §§ 2164.02 and 2107.01(III) and the Federal Circuit case law, which expressly points out that success in FDA trials is not required to satisfy the enablement requirement. *In re Brana*, 34 U.S.P.Q.2d 1436, 1442-3 (Fed. Cir. 1995).

The Office also defines "pharmaceutical" use to include *in vivo* diagnosis as well as treatment, and contends that use of the claimed pharmaceutical compositions as "*in vivo* diagnostics" is also not enabled. Yet, the Office again uses too rigorous a standard in considering the enablement of methods for the diagnosis of disease. For example, the Office finds the citation of *ex vivo* diagnostic methods by Ishidou, Eberhagen, Gelmetti, and Stowe to be insufficient because the methods were allegedly performed using cells taken from the animal to be diagnosed, rather than performed in the animal itself. (Office Action at page 15.) Applicants submit, however, that minimally invasive and *ex vivo* procedures are greatly preferred for the diagnosis of disease because they are less harmful, less costly, and do not require expensive and lengthy FDA clinical trials. For example, blood cell or lymphocyte diseases are routinely diagnosed using various *ex vivo* blood tests, (e.g., for HIV, leukemia, etc.). Cancer is typically diagnosed by a biopsy, which involves removing tissue from the body and testing it *in vitro*.

In addition, Applicants again note that in cases where such an *ex vivo* diagnostic procedure is not available, the enablement of possible *in vivo* diagnostic methods

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should be judged based on a correlation of the *ex vivo* data with a possible *in vivo* use. M.P.E.P. § 2164.02. Cell culture systems and *ex vivo* tests are frequently used to test the therapeutic or diagnostic potential of compounds, as the articles by Ishidou, Eberhagen, Gelmetti, and Stowe illustrate. Because these articles show an *ex vivo* effect in cell culture that correlates with a utility *in vivo*, the articles provide more than adequate evidence of enablement.

In view of these remarks, Applicants respectfully request the withdrawal of this rejection.

Claims 8, 9, and 24-26 Are Definite

The Office rejected claim 8, and claims 9 and 24-26, which depend from claim 8, as allegedly indefinite. (Office Action at pages 16-17.) The Office objected to the definition of R^3 in claim 8 because it recites that R^3 is "the chemical group, where R^3 is preferably a -C(=O) group or an -NH -C(=S) group." According to the Office, this represents more than one range of possible substituents. Applicants have amended claim 8 to recite that R^3 is a "carbonyl or thioamide group." Thus, Applicants request that this rejection be withdrawn.

Claims 1, 2, 4, 5, 8, 10-12, and 15-25 Are Novel

The Office rejected claims 1, 2, 4, 5, 8, 10-12, and 15-25 under 35 U.S.C. § 102(b), asserting that they are anticipated by Cook (WO 94/01448). (Office Action at pages 17-18.) The Office cites the compound of Cook at page 6, line 4, second structure. Applicants traverse this rejection.

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The compound at page 6, line 4, of Cook does not fall within the genus of conjugating compounds claimed in any of claims 1, 2, 4, 5, 8, 10-12, and 15-25 because in Cook, the equivalent of R^1 is not "a substituted or unsubstituted C_1 -C_{23} alkyl radical, which is straight-chain or branched and may contain double and/or triple bonds," as Applicants claim, but a heterocyclic ring fused to the nitrogen atom at position X. Such a fused ring system is not contemplated by the recitation of "a straight-chain or branched" substituent. Indeed, a ring is not a "straight chain," or a "branched" chain. In addition, no other compound disclosed in Cook anticipates any of Applicants' claims. Therefore, Applicants request the withdrawal of this rejection.

Claims 1, 8, 11, 13, 14, and 26 Are Nonobvious

The Office rejects claims 1, 8, 11, 13, 14, and 26 under 35 U.S.C. § 103(a), contending that they are obvious over Cook. (Office Action at pages 18-19.) Applicants traverse this rejection.

The Office's contention is based on its allegation that the structure at page 6, line 4, of Cook anticipates some of Applicants claims. (See above.) However, in the Cook compound, R^1 is not a straight chain or branched chain comprising 1-23 carbons, but is a heterocyclic ring fused to the nitrogen atom at position X. Therefore, this compound does not anticipate any of claims 1, 2, 4, 5, 8, 10-12, and 15-25, as described above.

Nothing in Cook teaches or suggests that one should substitute the straight chain or branched R^1 group of the instant invention for Cook's heterocyclic ring. For example, even claimed compounds in which R^1 is a 4-carbon substituted straight chain with the same substitutions as in Cook's 5-membered ring, X is nitrogen, and Y is a carbonyl,

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would be expected to have different structural and chemical properties from Cook's compound. First, a ring has a different shape than a straight or branched chain, and is restricted in motion. Second, the ring structure may have a different polarity than a straight or branched chain with the same nitrogen and carbonyl substituents because of the different way in which those substituents are arranged in space. Thus, this compound is insufficient to render Applicants' claims obvious.

More importantly, an analysis under § 103(a) requires that both the cited prior art and Applicants' claims be considered in their entirety. M.P.E.P. § 2141.03. Thus, the compound at page 6, line 4, of Cook cannot be considered alone, but Cook must be considered for what it teaches one of ordinary skill in the art as a whole. *Id.* It is impermissible to pick and choose elements from a disclosure that support a particular conclusion, while ignoring other teachings of the reference that may not support that conclusion. *Id.*; *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303 (Fed. Cir. 1983).

Pages 5 and 6 of Cook disclose many other types of modifications that are unrelated to the structure at page 6, line 4. Moreover, the compounds described at pages 5 and 6 of Cook are not designed to be the active conjugates themselves, but merely linkers used to attach a variety of other conjugate groups to the nucleic acid molecules. Pages 7-17 of Cook go on to describe how to attach various types of conjugates to these linkers.

The possible conjugates of Cook, in turn, are "amino acids, dipeptide mimics, sugars, sugar phosphates, and neurotransmitters or analogues thereof," as well as poly-hydroxypropylmethacrylamide, dextrans, polymaleic anhydride, cyclodextrins, starches,

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and polyethyleneimine. (Cook at page 1, lines 21-23; page 3, lines 3-11.) These classes of conjugates comprise hundreds or thousands of compounds of widely variable structure and chemical properties, as is readily apparent from an analysis of the disclosure at pages 7-17 of Cook. For example, Cook specifically lists 5 types of amino acid conjugates, 8 types of dipeptide mimetics, 12 types of sugars, and 11 types of sugar phosphates, while pointing out that the scope of the invention should not be limited to the named conjugates. (Cook at page 7, lines 4-8; page 7, line 33, to page 8, line 4; page 9, line 21-28; page 11, lines 7-19.) Thus, the disclosure of Cook does not provide one of ordinary skill in the art with a motivation to prepare Applicants' specific, claimed genera recited in claims 1 and 8 for increased cellular uptake of oligonucleotides.

Moreover, the Federal Circuit has repeatedly stated that to make *a prima facie* case of obviousness, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components in the manner claimed" (emphasis added). *In re Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002), quoting *In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). The Office has provided no evidence to show that the broad disclosure of Cook would lead one of skill in the art to the present claimed genus of compounds, and thus has failed to meet the substantial evidence standard of *In re Zurko*, 258 F.3d 1379, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Thus, Applicants respectfully request that this rejection be withdrawn.

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CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not submitted herewith to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: January 21, 2003

By: _____
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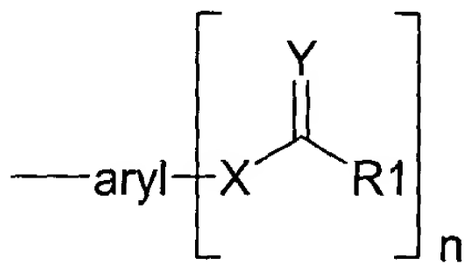
APPENDIX TO AMENDMENT OF JANUARY 21, 2003

Version Showing Changes Marked-Up

Amendments to the Claims:

1. (Amended) A conjugate, which comprises a molecule to be transported and at least one aryl radical of the formula I,



(I)

wherein

aryl is a group which contains at least one ring having an aromatic character;

X is O or N;

Y is O, S or NH-R^2;

R^1 is a substituted or unsubstituted C_1 -C_{23} alkyl radical, which [may be] is straight-chain or branched and may contain double and/or triple bonds;

R^2 is a substituted or unsubstituted C_1 -C_{18} alkyl radical which [may be] is straight-chain or branched and may contain double and/or triple bonds; and

n is an integer greater than or equal to 1,

wherein the aryl radical is attached to the molecule to be transported either directly via a chemical bond or indirectly via a chemical group, wherein the chemical group is not a CH_2-S group if the attachment is through an internucleotide phosphodiester bond of the molecule to be transported.

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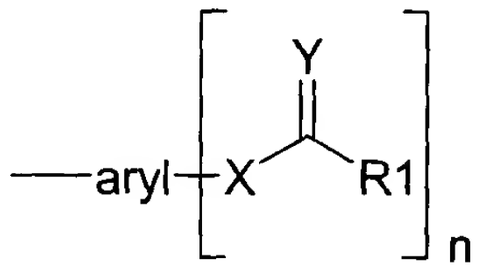
8. (Amended) A conjugate, which comprises a molecule to be transported and at least one aryl radical of the formula I,



(I)

wherein

aryl is a group which contains at least one ring having an aromatic character;

X is O or N;

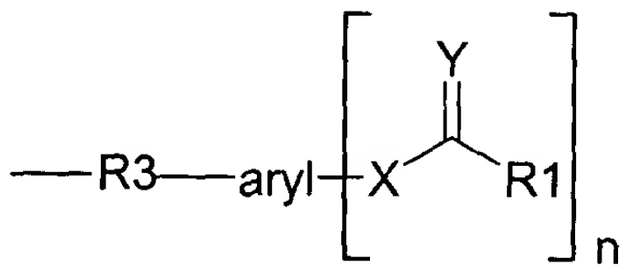
Y is O, S or NH-R^2 ;

R^1 is a substituted or unsubstituted C_1 -C_{23} alkyl radical, which [may be] is straight-chain or branched and may contain double and/or triple bonds;

R^2 is a substituted or unsubstituted C_1 -C_{18} alkyl radical which [may be] is straight-chain or branched and may contain double and/or triple bonds; and

n is an integer greater than or equal to 1,

wherein the aryl radical is attached to the molecule to be transported via a chemical group, and wherein the chemical group together with the aryl radical has the formula II



(II)

where aryl, X, Y and R^1 are as defined above and

R^3 is a carbonyl or thioamide group [the chemical group, where R^3 is preferably a -C(=O) group or an -NH -C(=S) group].

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